This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21

additional information.

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 87-R-0001
CUSTOMER NUMBER: 12

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

COPY FOR YOU
INFORMATION

University Of Utah
50 North Medical Drive, 1c311
Salt Lake City, UT 84132

Telephone: (801) -581-6840

resubmit 7 12/01/04
no changes
"A" by Dr. Watland
05/17/05

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Atached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessarv or use APHIS Form 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasc such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs	0	17	258	0	275
5. Cats	0	2	72	0	74
6. Guinea Pigs	0	80	207	522	809
7. Hamsters	0	11	10	0	21
8. Rabbits	0	232	703	0	935
9. Non-human Primates	0	0	4	0	4
10. Sheep	0	55	3	0	58
11. Pigs	0	6	58	0	64
12. Other Farm Animals	0	0	0	0	0
13. Other Animals					

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). A summary of all such exceptions is attached to this annual report. In addition to identifying the IACUC-approved exceptions, this summary in brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
xecutive Officer or Legally Responsible Institutional Official)

SI	NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL (*Type or Print*)	DATE SIGNED
		4/25/05

API is obsolete.)

APR 27 2005

FOR YOUR INFORMATION

Registration Number: 87-R-0001/12
Number of animals used in this study: 522
Species: Guinea pigs

Description of procedure

The procedure performed is a skin sensitization test. The animals utilized in the test experience slight pain that is occasionally more than momentary. It consists of slight skin irritation.

Scientific justification

Pain relievers in general, are anti-inflammatory and may interfere with optimization of the potential for detection of contact sensitization in this study design. Since inflammation is a component of the sensitization response being evaluated, introduction of agents that influence an inflammation response would most likely interfere with the evaluation of the potential of the test article to elicit a sensitization response.

Federal regulations requiring this procedure

International Standards Organization (ISO) 10993-1, parts 10 and 11

APR 2 7 2005

All redactions on this page are pursuant to (b)(6) & (b)(7)(c).

THE UNIVERSITY OF UTAH

Vice President for Research

201 S Presidents Circle Rm 210 Salt Lake City, Utah 84112-9011 (801) 581-7236 FAX (801) 585-6212

April 8, 2005

Richard Watkins, D.V.M.
Supervisory Animal Care Specialist
Western Region, Animal Care
2150 Centre Avenue, MS 3W11
Fort Collins, CO 80526

COPY F
INFORM

Reference: Registration # 87-R-0001, Customer # 12

Dear Dr. Watkins,

I am writing in response to your letter dated March 25, 2005 in which you requested additional information regarding our facility's annual report.

First, please find enclosed an amended annual report which was submitted electronically on March 2, 2005. This report corrects the previous submission received by APHIS on October 25, 2004.

Second, in regard to further clarification for the justification to withhold topical anesthetic or analgesic, I am enclosing a copy of a letter sent to [redacted] The letter responds to concerns raised by [redacted] in connection with the guinea pigs listed in category E and addresses specifically the reason that an anesthetic/analgesia would adversely affect the study results.

Finally, I am enclosing a copy of ISO 10993, part 10, section 6, which describes the maximization test method. While this document does not specifically indicate that pain and/or distress relieving drugs may not be used, it does specify the maximization method for use when investigating erythema and/or oedema reactions (see table 6). Please note our citation of ISO 10993 on Form 7023 is in response to item 6 of the Column E Explanation section which asks "What, if any federal regulations require this procedure?". Please refer to the letter mentioned above for a specific justification for not using pain relieving drugs.

Thank you for your consideration in this matter. Please contact us if you have any further questions.

R 1 1 2005

Enclosures

PDEF
Preclinical Drug Evaluation Facility

University of Utah
421 Wakara Way, Suite 318
Salt Lake City, Utah 84108
(801) 581-7178 Voice
(801) 585-3614 Fax

(b)(6), (b)(7)(C)

www address:
http://biotech.genetics.utah.edu/pdef/

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March 1, 2005

(b)(6), (b)(7)(C)

Dear (b)(6), (b)(7)(C)

I am writing in response to your letter dated February 17, 2005, based upon concerns raised by (b)(6), (b)(7)(C) regarding the annual USDA report. In regard to item #1, our current use of the Guinea Pig Maximization Test is limited to FDA submission/regulation, in particular evaluation of medical devices and compounds for biocompatibility assessment. The Murine Local Lymph Node Assay (LLNA) has been accepted as an alternative to the Guinea Pig Maximization Test by the EPA for use in evaluating certain chemicals based upon the ICCVAM/NIH publication 99-4494, February 1999. This publication presented the strength of the LLNA; however, the usefulness of the method for testing mixtures and extracts was not addressed in the proposal. Additionally, the EPA and EMEA guidance document state that the LLNA may not be appropriate for all types of test materials, such as certain metallic compounds, high molecular weight proteins, strong dermal irritants and materials that do not sufficiently adhere to the ear for an acceptable period of time during treatment. When using the LLNA, particular care should be taken to ensure that hydrophilic materials are incorporated into a vehicle system that wets the skin and does not immediately run off. Thus, wholly aqueous vehicles or test materials and runny liquids are to be avoided (EPA Health Effects Test Guideline – OPPTS 870.2600, Skin Sensitization). The materials that we evaluate under FDA and ISO Standards are aqueous and oil extracts of medical devices and thus would not be candidates for use in the LLNA. Therefore, the Guinea Pig Maximization Test is considered to be the most appropriate animal model to evaluate sensitization potential for devices and other compounds which employ aqueous extracts, as well as those that are liquid in nature.

In regard to item #2, I had performed a literature search using MEDLINE (September 26, 2003) with the key words "drugs", "medical devices", "pharmaceuticals", "guinea pigs", "drug effects", "pain", "distress", "animal testing alternatives", "anesthesia", "analgesia", "non-animal model", and "cell cultures" prior to protocol submission. I have since performed an additional literature search using MEDLINE (February 28, 2005) with the key words "analgesia", "anti-inflammatory response" and "guinea pigs". The years covered by these searches were 1965-present. Based upon these searches, I was unable to find an analgesia method which does not effect the inflammatory reaction. In addition, I have spoken to several veterinarians and veterinary pathologists, as well as a researcher from the Anesthesiology Department in the School of Medicine of the University of Utah. None of these individuals are aware of any alternatives which would not, in some way, affect the inflammatory response that we induce in this study design.

I hope that the information provided in this letter is sufficient. If there are any other issues that need to be addressed or if you require additional information regarding the issues addressed herein, please let me know.

Sincerely,

(b)(6), (b)(7)(C)

APR 1 1 2005

DRAFT INTERNATIONAL STANDARD ISO/DIS 10993-10.2

ISO/TC 194   Secretariat: DIN

Voting begins on   Voting terminates on
1993-11-11   1994-01-11

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION • МЕЖДУНАРОДНАЯ ОРГАНИЗАЦИЯ ПО СТАНДАРТИЗАЦИИ • ORGANISATION INTERNATIONALE DE NORMALISATION

ANSI Internat Doc Sec

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Biological evaluation of medical devices —

Part 10:
Tests for irritation and sensitization

Évaluation biologique des dispositifs médicaux —
Partie 10: Essais d'irritation et de sensibilisation

RECEIVED AT ANSI
Cover Ltr.
Encl.
NOV - 5
Sent to (b)(6), (b)(7)(C)
ANSI Staff (b)(6), (b)(7)(C)

UDC [615.46/.47].076:616-002

Descriptors: medical equipment, surgical equipment, surgical implants, dental equipment, dental materials, tests, biological tests, skin irritation.

In accordance with the provisions of Council Resolution 15/1993, this document is circulated in the English language only.

Conformément aux dispositions de la Résolution du Conseil 15/1993, ce document est distribué en version anglaise seulement.

To expedite distribution, this document is circulated as received from the committee secretariat. ISO Central Secretariat work of editing and text composition will be undertaken at publication stage.

Pour accélérer la distribution, le présent document est distribué tel qu'il est parvenu du secrétariat du comité. Le travail de rédaction et de composition de texte sera effectué au Secrétariat central de l'ISO au stade de publication.

APR 1 1 2005

THIS DOCUMENT IS A DRAFT CIRCULATED FOR COMMENT AND APPROVAL. IT IS THEREFORE SUBJECT TO CHANGE AND MAY NOT BE REFERRED TO AS AN INTERNATIONAL STANDARD UNTIL PUBLISHED AS SUCH.

IN ADDITION TO THEIR EVALUATION AS BEING ACCEPTABLE FOR INDUSTRIAL, TECHNOLOGICAL, COMMERCIAL AND USER PURPOSES, DRAFT INTERNATIONAL STANDARDS MAY ON OCCASION HAVE TO BE CONSIDERED IN THE LIGHT OF THEIR POTENTIAL TO BECOME STANDARDS TO WHICH REFERENCE MAY BE MADE IN NATIONAL REGULATIONS.

COPY F
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6.2 Maximization sensitization test

6.2.1. Principle

Assessment of the potential of the material under test to produce skin sensitization in the guinea pig.

6.2.2. Test material

If the test material is a solid or a liquid it shall be prepared according to the procedures described in annex A.

If the test material is an extract, it shall be prepared as described in annex B.

6.2.3. Animals and husbandry

Healthy young adult albino guinea-pigs of either sex from a single outbred strain, weighing 300 to 500g at the start of the test shall be used. If female animals are used they shall be nulliparous and non-pregnant.

The animals shall be acclimatized and cared for according to procedures described in annex C.

For testing powders or liquids, a minimum of ten animals shall be treated with the test material and a minimum of five animals will act as a control group. Additional animals shall be used for the preliminary test.

For testing extracts, a minimum of ten animals shall be treated with each extract and a minimum of five animals will act as a control for each solvent. Additional animals shall be used for the preliminary test.

NOTE It may be necessary to double the number of animals in order to confirm weak sensitizers. See OECD Guideline No.406.

6.2.4. Test procedure

6.2.4.1. Preparation

Clip the fur on all treatment sites, the day prior to treatment.

For intradermal injections inject 0.1ml per site.

For all topical applications, saturate a patch of filter paper of the appropriate dimensions with the test material and apply the patch to the clipped skin surface under a retaining dressing.

NOTE e.g. an occlusive dressing wound around the torso of the animal.

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6.2.4.2. Preliminary tests

NOTE The preliminary tests are intended to determine the concentrations of the test materials to be used in the main test described in 6.2.4.3.

Pretreat all animals with Freunds Complete Adjuvant.

Inject a range of concentrations of the test material (in the selected solvent) intradermally into at least two animals.

Select for the intradermal induction phase in the main test, the highest concentration that does not cause extensive destruction of the skin and does not otherwise adversely affect the animals.

Topically apply a range of concentrations of the test material to the flanks of at least three additional animals. Remove the occlusive dressings and patches after 24 h and assess the application sites for erythema and oedema using the grading given in table 7.

Select:

a) if possible, for the topical induction phase in the main test, the highest concentration that causes slight erythema but does not otherwise adversely affect the animals;

b) for the topical challenge phase in the main test, the highest concentration that causes no erythema.

6.2.4.3. Main test

6.2.4.3.1. Intradermal induction phase

Make a pair of 0.1 ml intradermal injections of each of the following, into each animal, at the injection sites (1, 2 and 3) as shown in figure 3 in the clipped intrascapular region.

(1) A 50 : 50 mixture of Freund's Complete Adjuvant mixed with the chosen solvent. Water for injection or physiological saline (BP,USP or equivalent) for water soluble substances. For non-aqueous soluble substances, examples of solvents are given in Annex B 2.10.

(2) The test material at the concentration selected in the preliminary tests, inject the control animals with the solvent alone.

(3) The test material at the concentration used in (2), emulsified in a 50 : 50 mixture of Freund's Complete Adjuvant and the solvent; inject the control animals with the solvent emulsified in adjuvant.

6.2.4.3.2. Topical induction phase

Seven days after completion of intradermal induction phase, administer the test material by topical application to the intrascapular region of each animal, using 20 mm x 40 mm filter paper, so as to cover the intradermal injection sites. Use the concentration selected in 6.2.4.2.a). Secure with an occlusive dressing. Remove the dressings and patches after 48 +/- 2 h.

Treat the control animals similarly, using the solvent alone.

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If the maximum concentration that can be achieved in 6.2.4.2.a) does not produce irritation, pre-treat the area with 10% sodium lauryl sulphate in petrolatum massaged into the skin 24 +/- 2h before the topical induction patch is applied. Treat the control groups similarly.

6.2.4.3.3. Challenge phase

At least 14 days after completion of the topical induction phase, challenge all test and control animals with the test material. Administer the test material by topical application to one flank of each animal using appropriate patches soaked in the test material at the concentration selected in 6.2.4.2.b). Secure with an occlusive dressing. Remove the dressings and patches after 24 +/- 2h.

NOTE Dilutions of this concentration may also be applied to other untreated sites in a similar manner.

6.2.5. Observation of animals

Observe the appearance of the challenge skin sites of the test and control animals 24 h, 48 h and 72 h after removal of the dressings. Describe and grade the skin reactions for erythema and eschar according to the grading given in table 6 for each challenge site and at each time interval observed.

6.2.6. Evaluation of results

Grades of 1 or greater in the test group generally indicate sensitization, provided grades of less than 1 are seen on control animals. If grades of 1 or greater are noted on control animals, then the reactions of test animals which exceed the most severe control reaction are presumed to be due to sensitization.

NOTE Occasionally, test animals may have a greater incidence of skin reactions which are comparable in intensity to controls, without a single animal being more reactive. In these instances, a rechallenge may be necessary to clearly define the response. If necessary a rechallenge shall be carried out approximately 7 days after the first challenge. The method used shall be as described for the first challenge, using the other flank of the animal.

6.2.6. Presentation of results

The test report shall include:

a) a description of the test material(s) or device;
b) the intended use/application of the test material(s) or device;
c) a detailed description of the method employed in preparing the test material or device;
d) the test animals;
e) method of application to the test sites;
f) how the site readings were performed and a record of the observations;
g) assessment of the results.

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Table 6 - Classification system for skin reactions

Reaction	Numerical Grading
Erythema	
No erythema	0
Slight erythema	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema to slight eschar formation	4
Oedema	
No oedema	0
Slight oedema	1
Well-defined oedema	2
Moderate oedema	3
Severe oedema	4

NOTE 1. Other adverse changes of the skin sites shall be recorded and reported.

NOTE 2. For the purposes of standardization the grading system has been modified from the original method.

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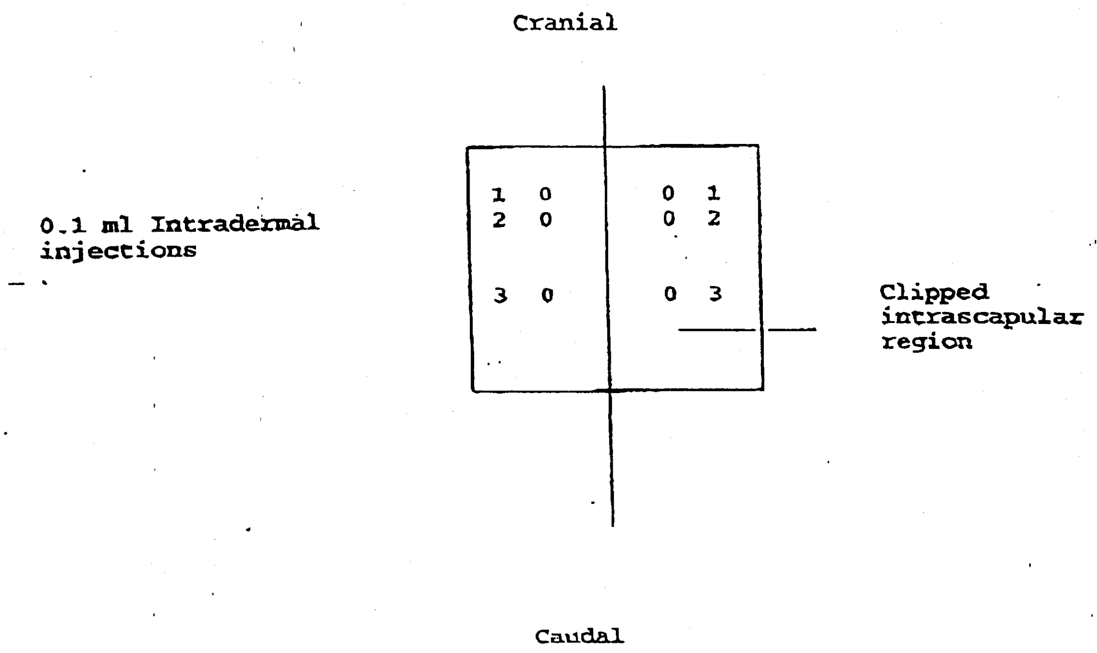
Figure 3 - Location of intradermal injection sites



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